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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,748	12/21/2001	Oluwole T. Aloba	2911.600	5061

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,748	ALOBA ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-47* is/are pending in the application.

4a) Of the above claim(s) *12-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-11, and 46-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed November 17, 2003 have been entered.

The cancellation of claims 2-3 in amendments filed November 17, 2003 is acknowledged.

The addition of claims 46-47 in amendments filed November 17, 2003 is acknowledged.

The outstanding rejections under 35 USC 112 are withdrawn in view of the amendments filed November 17, 2003.

Claims 1 and 4-47 are pending.

Claims 12-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claims 1, 4-11, and 46-47 have been examined herein to the extent they read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 are 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for organic acids listed in page 9 of the instant specification as the inhibitor of hydrolysis, does not reasonably provide enablement for other organic acid as inhibitors of hydrolysis. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define an organic acid as suitably used as "inhibitor of hydrolysis". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of examples are set forth as "inhibitor of hydrolysis" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds

required. It is noted that some organic acids, such as methanesulfonic acid, are actually good catalysts of acid-catalyst hydrolysis of esters (See March, page 334). In other words, some acids are the promoter of hydrolysis instead of the inhibitors of it. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "inhibitor(s) of hydrolysis", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070), reference of record.

Stein teaches a unit dose composition containing estradiol 3-position derivatives including estradiol-3-acetate (See col. 2, lines 9-25; particular the compound of Formula I; also col. 8, lines 6-27, Example 3). Stein also teaches estradiol-3-acetate as useful in treating menopausal syndrome (See col. 6, line 58-65). Stein also teaches the estradiol derivative composition may be formulated into oral dosage form such as tablets, or capsules (See col. 6, line 22). Stein also teaches various conventional carriers, such as

suspending agents, and lubricants, can be incorporated into the composition (See col. 6, line 28-29).

Stein does not expressly teach the composition containing estradiol-3-acetate specifically.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate estradiol-3-acetate into the unit dose composition of Stein.

One of ordinary skill in the art would have been motivated to incorporate estradiol-3-acetate into the unit dose composition of Stein. It is known that estradiol 3-position derivatives can be formulated into oral unit dose composition such as tablet and capsule. Formulating any known estradiol 3-position derivatives, such as estradiol-3-acetate, into an oral dosage form such as tablet or capsule for the treatment of menopausal syndrome would have been reasonably expected to be useful.

Claims 4, 6-9, and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070) as applied to claims 1-3, 5, and 10-11 above, and further in view of Remington (Remington: The Science and Practice of Pharmacy, 19th ed., 1995, pages 1413, 1623-1626), March (Advanced Organic Chemistry, 3rd ed., 1985, page 334-338), and Wolfe et al. (Journal of Lipid Research, 2000;41:368-375).

Stein suggests estradiol-3-acetate oral unit tablet or capsule composition.

Stein does not expressly teach the moisture content of the composition as less than or equal to 8%. Stein does not expressly teach the employment of an inhibitor of hydrolysis such as acetic acid. Stein does not expressly teach the additional medicament such as progestational agent is incorporated into the unit dose composition. Stein does not expressly teach the dosage unit is prepared by granulation method.

Remington also teaches that various granulation methods are well-known in the art in tablet preparation (See page 1623-1626).

March teaches the process of acidic-catalyst hydrolysis of ester as completely reversible and symmetrical (See page 335, second paragraph). March also teaches that hydrolysis occurs only when the equilibrium is shifting to the right (See page 334).

Wolfe et al. teaches that the combination of estrogen and medroxyprogesterone is useful as hormonal replacement therapy, which has the benefits of reducing the VLDL and triglyceride levels (See page 374, col. 1, last paragraph to col. 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an inhibitor of hydrolysis such as acetic acid and a secondary agent, such as progestational agent to the composition of Stein. It would have been obvious to one of ordinary skill in the art at the time the invention was made to keep the moisture content as below 8%. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition through the process of granulation.

One of ordinary skill in the art would have been motivated to incorporate an inhibitor of hydrolysis such as acetic acid and a secondary agent, such as progestational agent to the composition of Stein. Since the products of 17β-estradiol-3-acetate hydrolysis are acetic acid and 17β-estradiol, adding acetic acid into the composition will help inhibiting the shifting of equilibrium to the right as taught in March. Therefore, incorporating acetic acid into the composition of Stein would have been considered as obvious to one of ordinary skill in the art since the addition of acetic acid would have been reasonably expected to inhibit r slow down the hydrolysis process. Optimizing the moisture content to be less than 8% would be considered obvious as being within the purview of skilled artisan, absent evidence to the contrary (See discussion below). Furthermore, based on Wolfe, it is known that the combination of estrogen and medroxyprogesterone, progestational agent, are useful in treating menopausal syndrome. Therefore, incorporating a progestational agent to an estradiol composition would have been reasonably expected to be useful in hormonal replacement therapy.

Response to Arguments

Applicant's arguments filed November 17, 2003 averring Stein not suggesting the herein claimed composition have been fully considered but they are not persuasive. Stein clearly teaches that the herein claimed compound, 17β-estradiol-3-acetate is useful as treatment for menopausal disorders when administered orally (See col. 6, lines 58-65). In addition, Stein also teaches such compound can be formulated into a

pharmaceutical composition. Although Stein teaches an improved way to synthesize the herein compound and its derivatives, it is not the basis of the rejection set forth in the previous office action mailed July 15, 2003.

Applicant's remarks in the declaration filed November 17, 2003 with regard to the improved bioavailability of orally administered 17β-estradiol-3-acetate over 17β-estradiol have been considered, but are not found persuasive. Applicant's statements in paragraph 5, page 2 of the declaration filed November 17, 2003 states "I do not believe that Stein et al. recognized the significant improvement in the relative bioavailability of estradiol found when 17β-estradiol-3-acetate is administered in oral preparation" are considered but are not found persuasive. Stein et al. clearly teaches the herein claimed compound, 17β-estradiol-3-acetate is useful as treatment for menopausal disorders when administered orally [emphasis added] (See col. 6, lines 58-65). Since Stein et al. teaches oral route of administration of the herein claimed compound, applicant's arguments are considered moot. Furthermore, the unexpected benefit demonstrated is to compare 17β-estradiol and the prodrug of 17β-estradiol (the ester, or acetate, of 17β-estradiol). It is not clear if it is a comparison to the closest prior art since the bioavailability of 17β-estradiol is not the basis of outstanding rejection set forth in the previous office action mailed July 15, 2003.

Applicant's rebuttal arguments filed November 17, 2003 averring hindsight reasoning is applied in the rejection have been considered, but are not found persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Stability testing is routinely performed a pharmaceutical composition is formulated. And any factors that would affect the stability of the composition will be optimized. In the instant case, the moisture level of the composition will be optimized because ester is known to be hydrolyzed in the presence of water. Therefore, optimized the level of moisture is seen to be obvious as being within the purview of skilled artisan.

Applicant's arguments filed November 17, 2003 with regard to silica gel is considered moot in view of the new ground of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

2/22/04